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USE OF PHYSOSTIGMINE BY THE INTRAVENOUS, INTRAMUSCULAR, AND ORAL ROUTES IN THE THERAPY OF ANTICHOLINERGIC DRUG INTOXICATION

by

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May 1976

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
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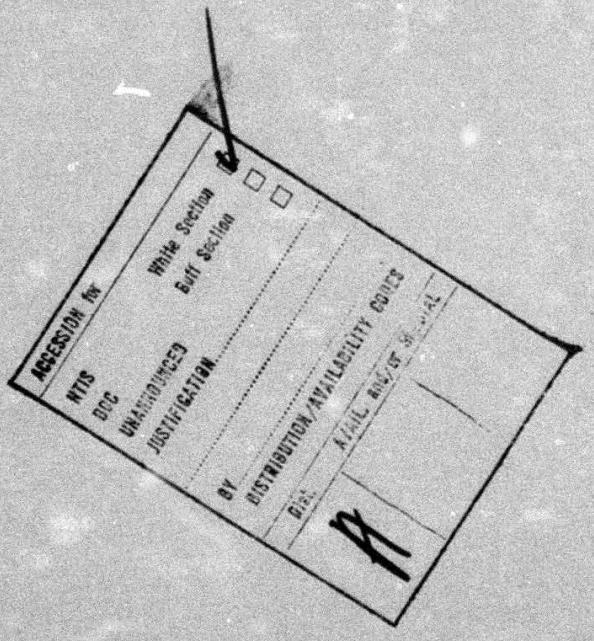

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Physostigmine was administered by three routes (intravenous, intramuscular, and oral) to treat intoxication by anticholinergic compounds in man. The drug by all routes of administration is effective. There are several reasons why the intravenous route of administration is not preferable for routine use.

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PREFACE

The work described in this report was authorized under Project/Task 1W762710AD2503, Medical Defense Against Chemical Agents/Prophylaxis and Therapy for Incapacitating Agents. This work was started in July 1968 and completed in May 1975.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

Acknowledgments

We wish to thank James S. Ketchum, M.D., for permission to use two of the case histories; the nurses and aidmen of the Clinical Research Branch, not only for the ward care of the subjects but also for assistance in data tabulation; and Marion P. Royston for editorial assistance.

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USE OF PHYSOSTIGMINE BY THE INTRAVENOUS, INTRAMUSCULAR, AND ORAL ROUTES IN THE THERAPY OF ANTICHOLINERGIC DRUG INTOXICATION

I. INTRODUCTION.

The use of physostigmine (as the elixir of the Calabar bean) as an antidote to the toxic effects of belladonna-like compounds was first reported over a century ago.[1] This remained relatively unnoticed until Forrer and Miller[2] reported success in reversing the effects of high doses of atropine with physostigmine. Later, several experimental[3,4] and clinical studies[5-7] added to our knowledge of this antidotal action of physostigmine.

Several relatively recent reports indicate that physostigmine can reverse the effects of large doses of other compounds, such as phenothiazine[8] and certain tricyclic antidepressants,[9-11] which appear to have some degree of cholinergic blocking activity. Although a major use of nontopically administered physostigmine in clinical medicine continues to be to reverse self-induced drug intoxication, it is also commonly used postoperatively to counteract the side effects of anticholinergic drugs given as preanesthetic medication.[12,13]

Earlier reports from this laboratory indicated that an optimal dose of physostigmine was 50 to 60 μg/kg given intramuscularly.[3,4] At that time, physostigmine was available commercially in a preparation containing 4 mg/ml* and this dose represented a volume of about 1 ml for a 70-kg man. At present, physostigmine is available only in a preparation containing 1 mg/ml,** and a volume of 4 ml is rather large for intramuscular use.

The manufacturer recommends 1 to 3 mg as the appropriate intravenous dose. Whether the optimum dose is within this range and the equivalency of intramuscular and intravenous doses are unresolved points.

This report compares our experiences with intravenous, intramuscular, and oral physostigmine.

II. METHODS.

A. Subjects.

The subjects were US Army enlisted men who volunteered to participate after the purpose and possible hazards of the investigations had been fully explained to them. The general methods of the studies were the same as those previously described.[3,4] The subjects came to the ward the evening before the study and remained for 24 hours after their clinical status and performance test scores had returned to baseline. After a light breakfast, they received an anticholinergic drug (intravenously or intramuscularly) and, at the time(s) specified under results, were given physostigmine (intravenously, intramuscularly, or orally). At intervals varying from 15 minutes in some studies to 4 hours in others, their heart rate, blood pressure, pupil size, and temperature were measured, and they were given a test of performance. Only the test of performance and heart rates are reported. At all times, they were under the direct observation of a nurse or well-trained aidman, and a physician was in attendance.

* Physostigmine salicylate–S. F. Durst and Company, Philadelphia, Pennsylvania. (Although no longer manufactured, this was the preparation used in this study.)

** Antilirium® – O'Neal, Jones, and Feldman, Inc., St. Louis, Missouri.

B. Performance Measures.

Several performance measures were used in some of these studies, but the one reported is the Number Facility (NF) test. This is a standardized 3-minute addition task,[3,4] and the scores after drug are expressed as a percentage of the mean of the five highest of 25 predrug scores. This score correlates well with the clinical condition of the subject: a subject who scores less than 10% is usually markedly confused and disoriented, whereas a subject scoring about 75% usually appears normal, although defects in thinking may be detected on careful examination.

C. Protocol for Administration of Anticholinergic Drugs and Physostigmine.

1. Scopolamine Hydrobromide. Six subjects were given 10 μg/kg of scopolamine hydrobromide intravenously; 1.5 hours later, two of the subjects were treated intravenously with 15 μg/kg of physostigmine. The four untreated subjects served as controls.

2. Atropine Sulfate. The protocol for studies with 150 μg/kg of atropine sulfate given intramuscularly and followed by treatment with physostigmine given intravenously is shown below:

No. of subjects	Time of treatment hr after atropine	Dose μg/kg
2	2	15
1	2	30
	4	15
1	2	30
3	2	45

3. 3-Quinuclidinyl Benzilate (QNB). Eight subjects were given 7 μg/kg of QNB intramuscularly. Four of these men served as controls; the other four were treated at varying intervals with physostigmine intramuscularly or orally, or both, as follows:

One subject received 90 doses orally, ranging from 1 to 4 mg per dose, for a total dose of 207 mg over 71 hours.

One subject received 40 doses orally, for a total dose of 80 mg over 37 hours.

One subject received three intramuscular doses (total, 11 mg), followed by three oral doses (total, 12 mg), over 42 hours.

One subject received two intramuscular doses (total, 7 mg), followed by six oral doses (total, 24 mg), over 43 hours.

D. Drugs.

Scopolamine hydrobromide and atropine sulfate were obtained from commercial sources. QNB was synthesized in the Chemical Laboratory, Edgewood Arsenal, and pharmaceutically prepared by Biomedical Laboratory.

Physostigmine was obtained from commercial sources. The intravenous preparation contained 1 mg/ml.* The intramuscular preparation contained 4 mg/ml.** Physostigmine given orally† was administered as a freshly prepared solution (1 mg/ml) or as tablets (1 mg each) prepared in this laboratory.

III. RESULTS.

A. Scopolamine Hydrobromide.

The serial mean scores on the NF test of the two subjects who received 10 μg/kg of scopolamine hydrobromide intravenously and 1.5 hours later were treated with physostigmine salicylate, 15 μg/kg, intravenously are shown in figure 1. Improvement occurred within several minutes and maximal therapeutic effect was noted 15 to 30 minutes after administration of the antidote. By 1.5 to 2 hours later, their status was similar to that of untreated subjects. The heart rates of the two subjects at time of treatment were 52 and 50 beats per minute (bpm). Thirty minutes after they received physostigmine their heart rates were 44 and 48 bpm, which decreased to 44 and 40 bpm at 45 minutes and then increased over the next several hours. This bradycardia was due to scopolamine rather than to physostigmine.

B. Atropine.

The seven subjects given 150 μg/kg of atropine sulfate intramuscularly were treated 2 hours later with either 15, 30, or 45 μg/kg of physostigmine intravenously. Their scores on the NF test and changes in heart rate are shown in figures 2 through 5. As there were no control subjects in this particular study, the range of the mean data from a previous study[4] in which subjects received 125 or 175 μg/kg of atropine sulfate intramuscularly are shown for comparison. The smallest dose of physostigmine produced a moderate improvement in the subjects' mental status starting a few minutes after its administration. These subjects had much less tachycardia than expected and the change caused by the antidote is difficult to assess (figure 2).

The data for the two subjects given 30 μg/kg of physostigmine are shown separately because one subject was treated a second time 2 hours later (figures 3 through 4). The effects of atropine on both subjects were dramatically reversed, but the therapeutic effect lasted less than 2 hours. One subject became quite restless and uncomfortable at this time and was given an additional 15 μg/kg of physostigmine intravenously. Again, his delirium was markedly reversed, but the reversal lasted less than an hour. The time course of the slowing of the atropine-induced tachycardia was somewhat shorter than the reversal of mental effects caused by physostigmine, as an hour after physostigmine the heart rates appeared to return to the untreated course.

The largest dose of physostigmine also produced a rapid and dramatic reversal of the central effects of atropine, and improvement was noticeable for 3 to 4 hours, which is longer than that caused by the lower doses (figure 5). The heart rate slowing also was more prolonged than that caused by lower doses. The degree of effectiveness of this dose on both mental changes and heart rate was comparable to that reported by Crowell and Ketchum[3] when they used 60 μg/kg of physostigmine intramuscularly to treat the effects of 175 μg/kg of atropine sulfate.

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* Antilirium ® – O'Neal, Jones, and Feldman, Inc., St. Louis, Missouri.

** Physostigmine salicylate S. F. Durst and Company, Philadelphia, Pennsylvania.

† Physostigmine salicylate–S. B. Penick and Company, New York, New York.

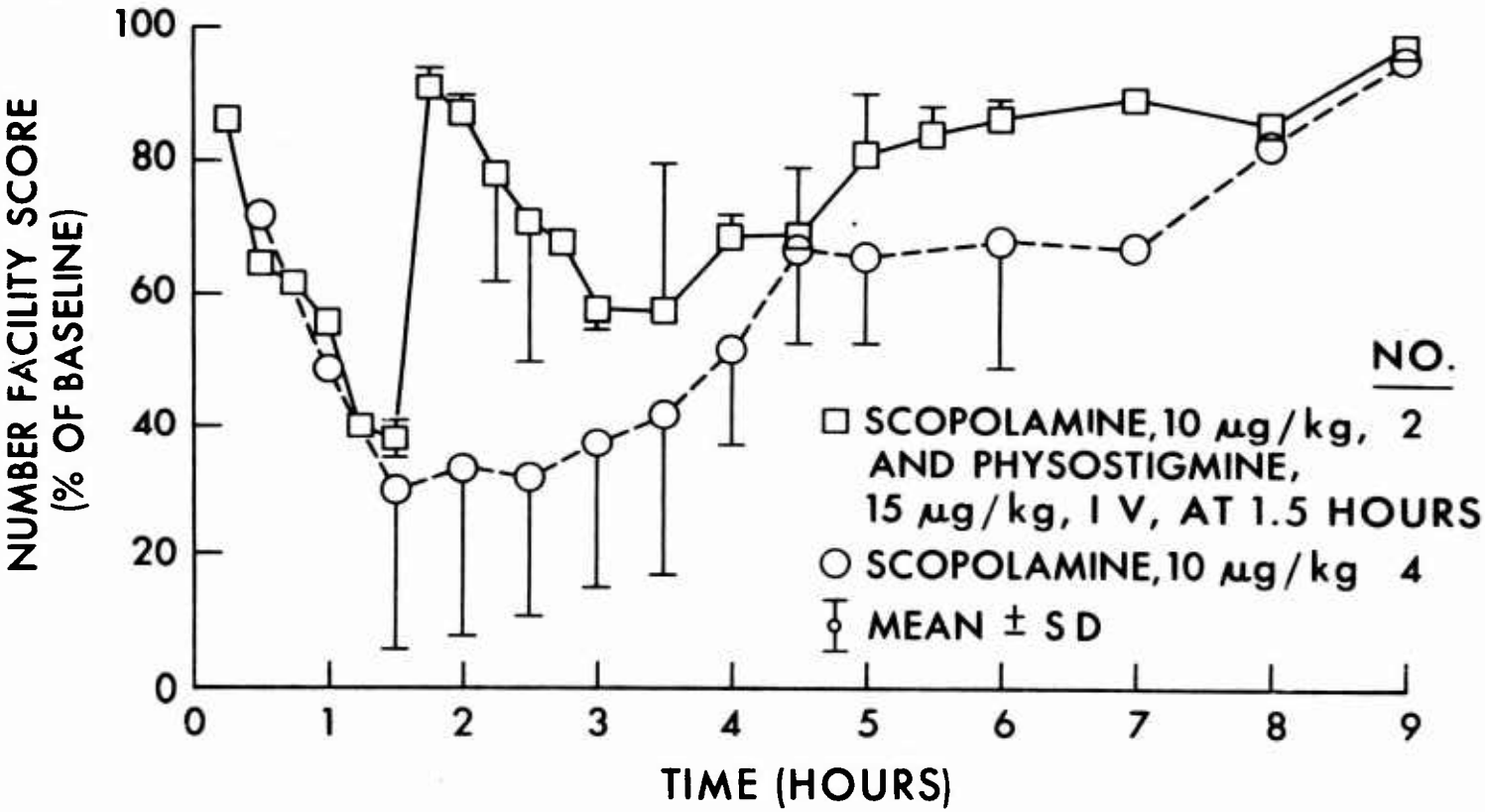

Figure 1. Mean NF Scores of Four Subjects Who Received 10 µg/kg of Scopolamine, Intravenously, Compared with Mean Scores of Two Subjects Who Were Then Treated with Physostigmine Salicylate, 15 µg/kg, Intravenously, After Scopolamine

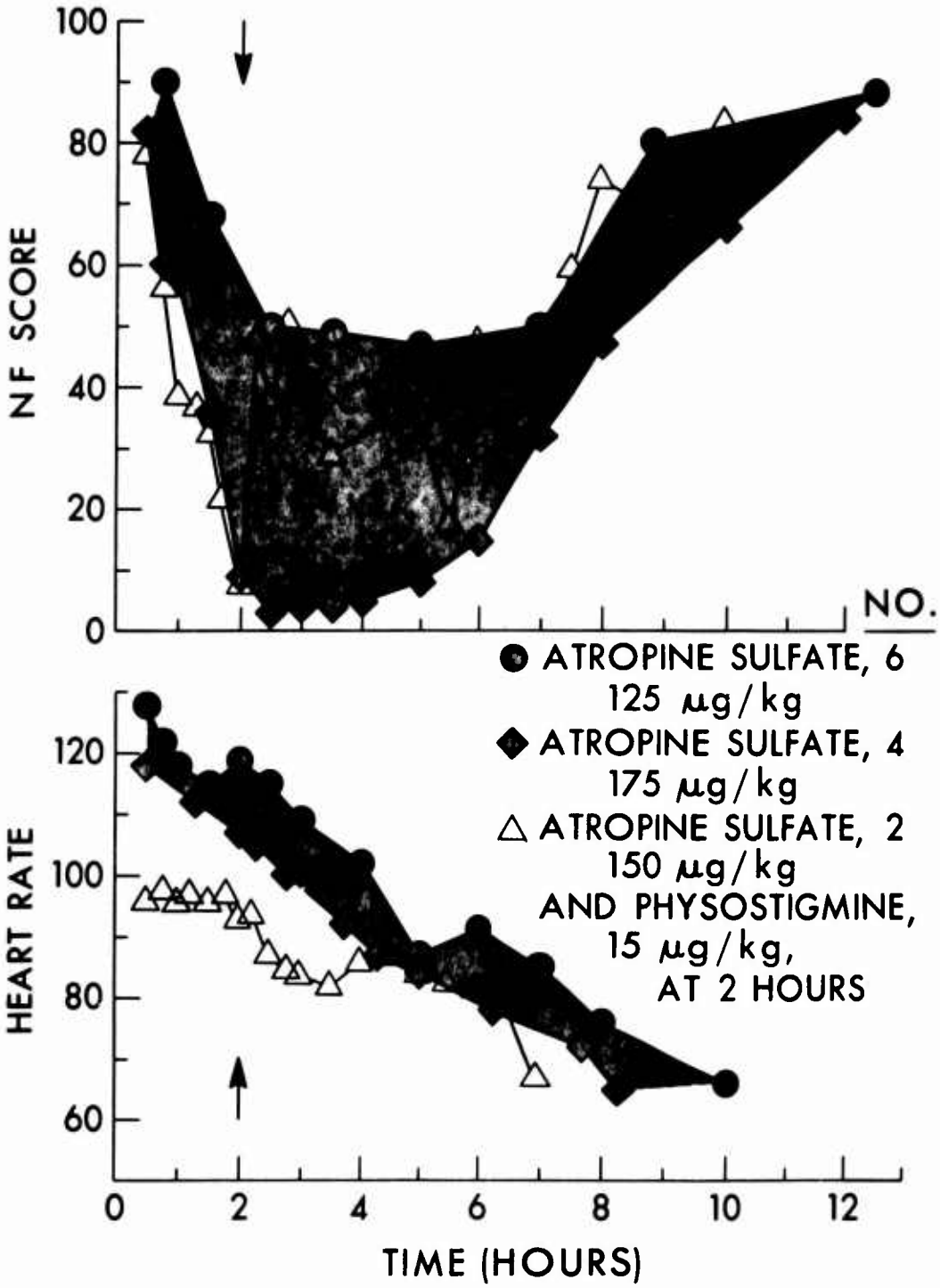

Figure 2. Mean NF Scores and Heart Rates of Two Subjects Who Received Atropine Sulfate, 150 µg/kg, Intramuscularly, and Were Treated with Physostigmine Salicylate, 15 µg/kg, Intravenously at 2 Hours

The shaded area is the range of measures between the mean of a group of six subjects who received atropine sulfate, 125 µg/kg, and the mean of a group of four subjects who received 175 µg/kg, intramuscularly.

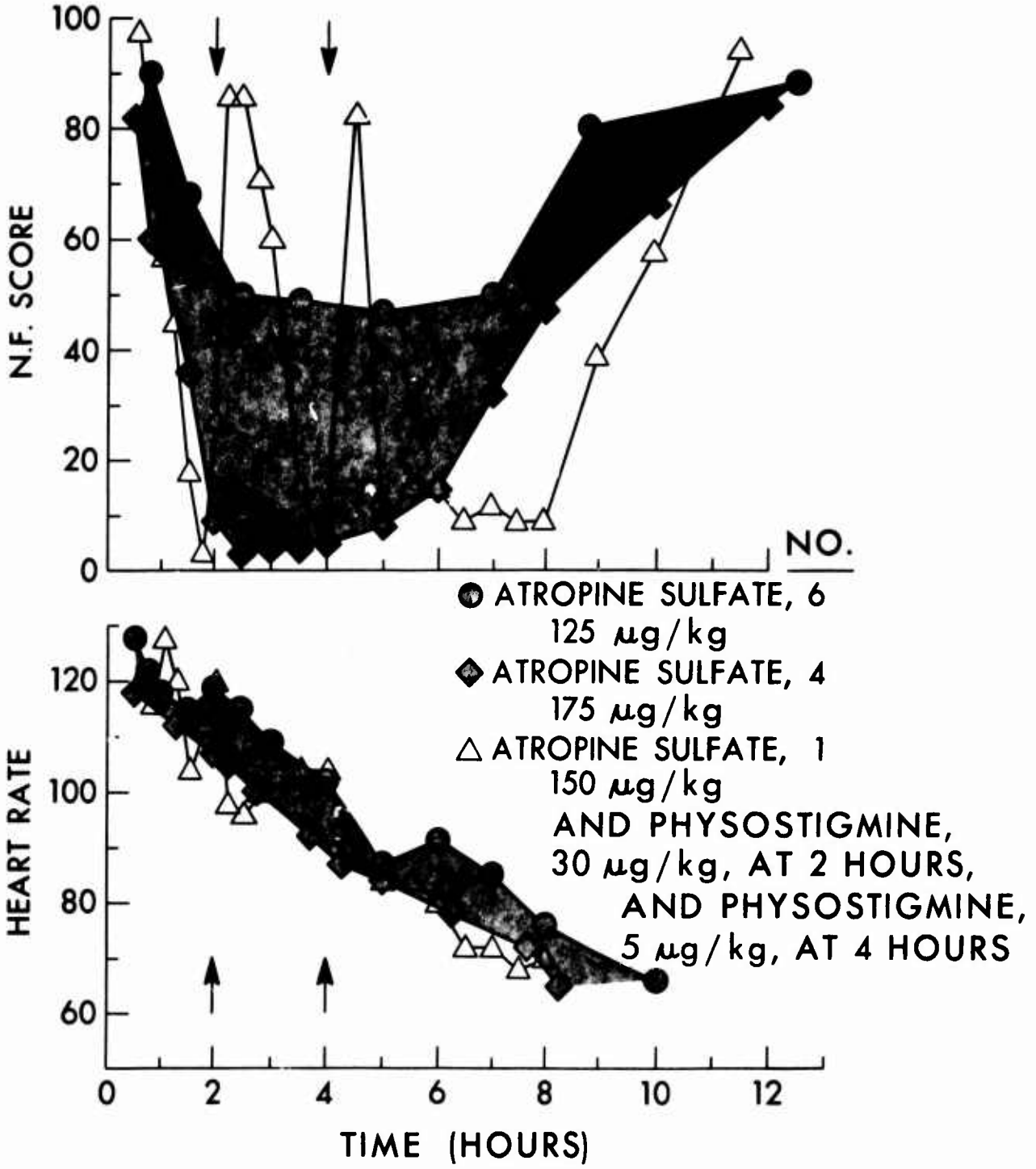

Figure 3. NF Scores and Heart Rates of Subject Who Received Atropine Sulfate, 150 µg/kg, Intramuscularly, and Physostigmine Salicylate, 30 µg/kg 2 Hours Later and 15 µg/kg 4 Hours Later

The shaded area is the range of measures between the mean of a group of six subjects who received atropine sulfate, 125 µg/kg, and the mean of a group of four subjects who received 175 µg/kg, intramuscularly.

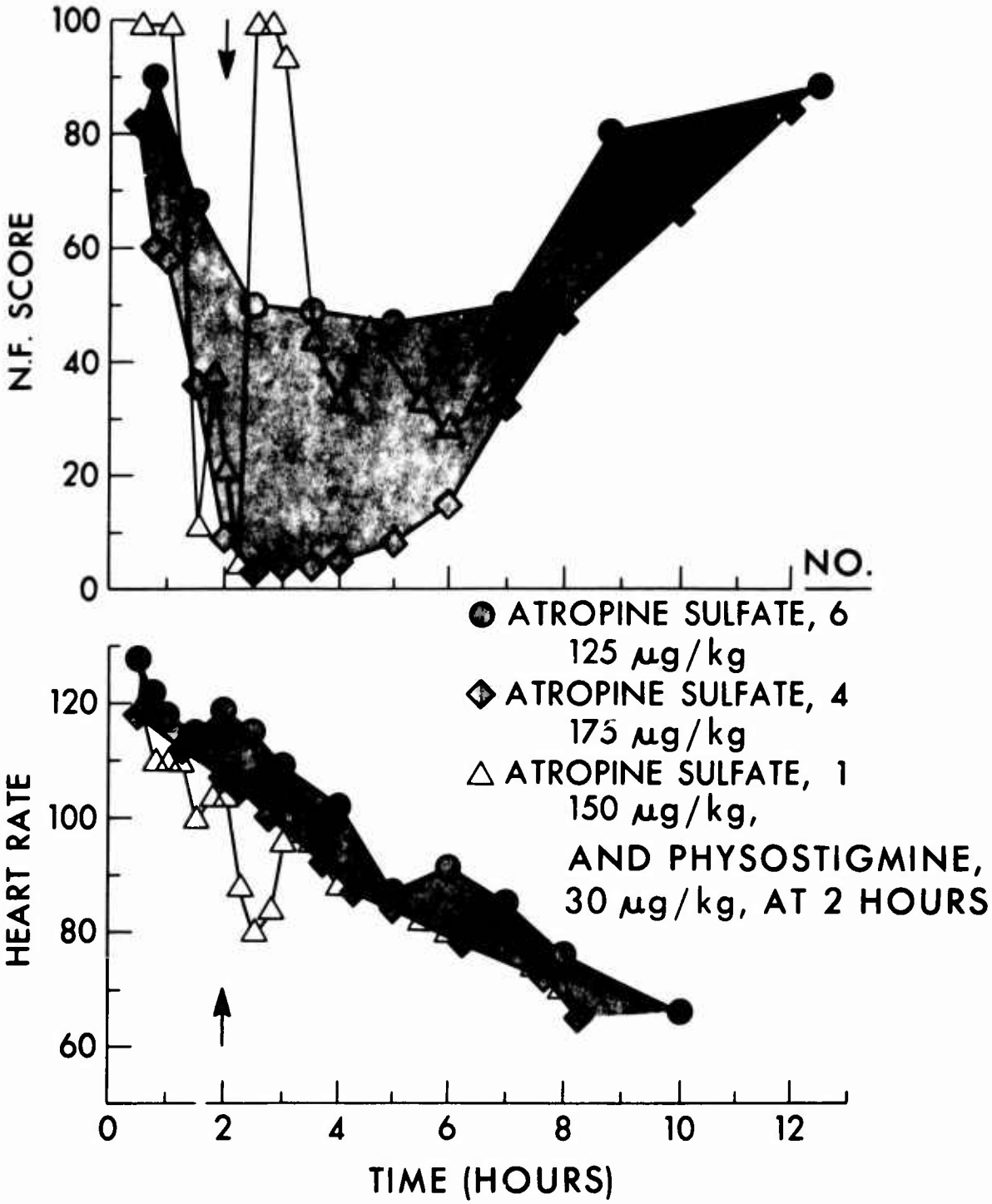

Figure 4. NF Scores and Heart Rates of Subject Who Received Atropine Sulfate, 150 µg/kg, Intramuscularly, and Physostigmine Salicylate, 30 µg/kg, 2 Hours Later

The shaded area is the range of measures between the mean of a group of six subjects who received atropine sulfate, 125 µg/kg, and the mean of a group of four subjects who received 175 µg/kg, intramuscularly.

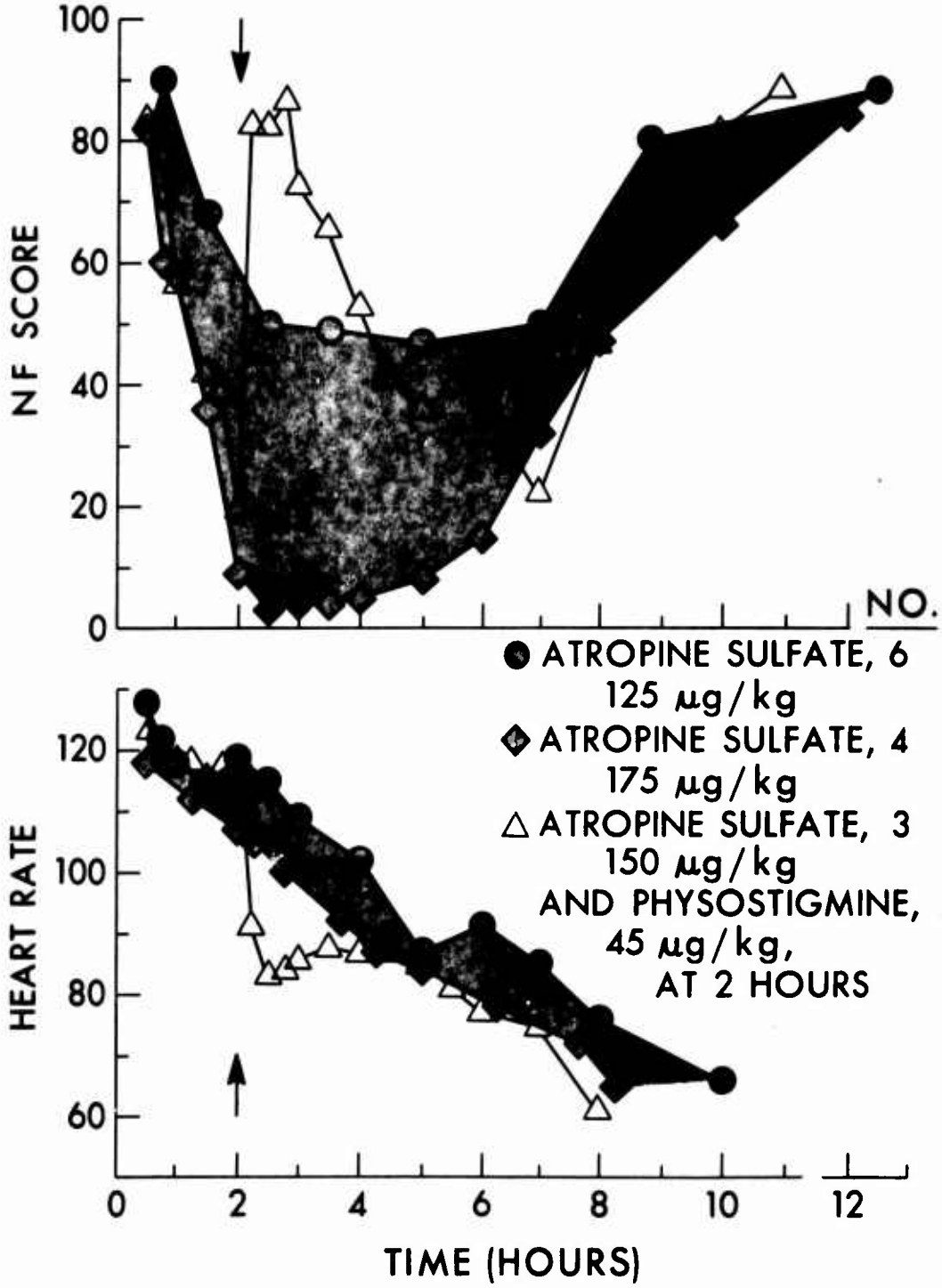

Figure 5. Mean NF Scores and Heart Rates of Three Subjects Who Received Atropine Sulfate, 150 µg/kg, Intramuscularly, and Were Treated with Physostigmine Salicylate, 45 µg/kg, Intravenously, at 2 Hours

The shaded area is the range of measures between the mean of a group of six subjects who received atropine sulfate, 125 µg/kg, and the mean of a group of four subjects who received 175 µg/kg, intramuscularly.

C. QNB.

QNB is a cholinergic blocking compound which produces effects in man identical to but longer lasting than those of atropine.[14] Several subjects were treated with physostigmine, orally or intramuscularly, to reverse these effects.

A subject was given 7 μg/kg of QNB, intramuscularly, without therapy. Four weeks later he received the same dose of this compound and was given physostigmine orally for 71 hours, beginning 1 hour after QNB. Each dose was preceded by an evaluation by a physician who increased or decreased the dose or the interval of dosing. He examined the patient for signs of cholinergic toxicity or cholinergic blocking activity (mental status, heart rate, muscular fasciculations, etc.). The subject's serial NF scores are shown in figure 6. During the first few hours there was no difference between his clinical status in the study when he was not treated and in the study when he was. This may have been because the dose of physostigmine was inadequate (five doses of 1.5 mg each over 4 hours) or, as has been suggested previously,[3] because the toxic effects of QNB are relatively resistant to therapy in the early stages. When the dose of physostigmine was increased and given regularly (e.g., 5 to 15 hours, 24 to 30 hours, and 38 to 70 hours – figure 6) the subject's clinical status was close to normal. When the dose of physostigmine was decreased or given less frequently, the subject relapsed into a semi-delirious state (e.g., 15 to 22 hours and 30 to 36 hours) and undoubtedly would have followed the untreated pattern if therapy had not been increased. He received 207 mg of physostigmine during the 71 hours of therapy.

A second subject was given physostigmine orally in a dose of 2 mg per hour (with occasional extra doses) for 37 hours after receiving 7 μg/kg of QNB intramuscularly. Again, the subject was thoroughly evaluated before each dose was given; in several instances (9.5 and 10.5 hours), extra doses were given. His NF scores are shown in figure 7. The initial marked decline in performance shown by the previous subject was somewhat averted by this regimen and the subject's status in general was much better than that of the untreated subjects. Whether the lack of relapse, after therapy was stopped at 37 hours, was because of accumulation of physostigmine or whether it was because this subject was less responsive to the effects of QNB is not clear. The relapse shown by most subjects within an hour or two after discontinuance of physostigmine suggests the latter. This subject received 80 mg of physostigmine during 37 hours.

Another subject received 7 μg/kg of QNB intramuscularly and was treated with physostigmine both intramuscularly and orally (figure 8). His serial scores are compared with those shown in figure 7 of four untreated subjects given the same dose of QNB. At 5 hours, 3 mg of physostigmine intramuscularly caused a moderate improvement, and 4 mg intramuscularly at 11 hours caused a greater response. The same dose at 36 hours produced a similar effect. This dose given orally 2 hours later (38 hours) appeared to cause little change, but two more oral doses at 2-hour intervals caused a marked improvement by 43 hours. This would probably have been sustained had treatment been continued, but therapy and testing were temporarily discontinued to allow the subject an uninterrupted sleep.

The data on a second subject treated similarly are shown in figure 9. This subject was more severely affected by the same dose of QNB (note courses of untreated subjects between 15 to 34 hours). He had less response to 3 and 4 mg of physostigmine given intramuscularly at 11 and 34 hours), but did show a steady improvement when three hourly doses of 4 mg of physostigmine were given orally between 38 to 40 hours. A relapse occurred when the dose was withheld at 41 hours, but resumption of dosing at 42 and 43 hours caused improvement again. At this point, the study was interrupted so that the subject could sleep.

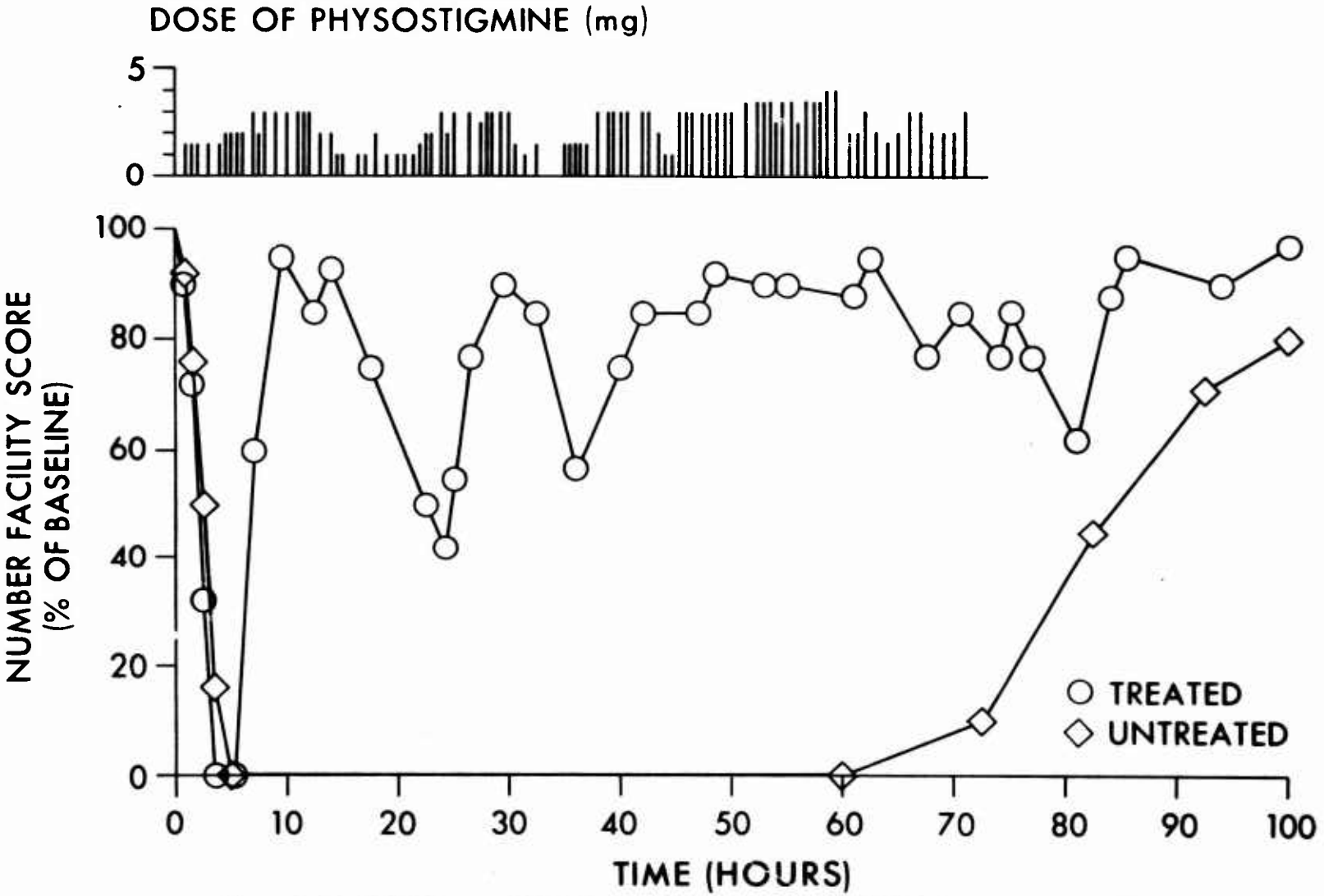

Figure 6. Serial NF Scores of Subject Who Received 7 μg/kg of QNB, Intramuscularly, Twice On one occasion, he was untreated and, on the second, he was treated with physostigmine orally, as shown.

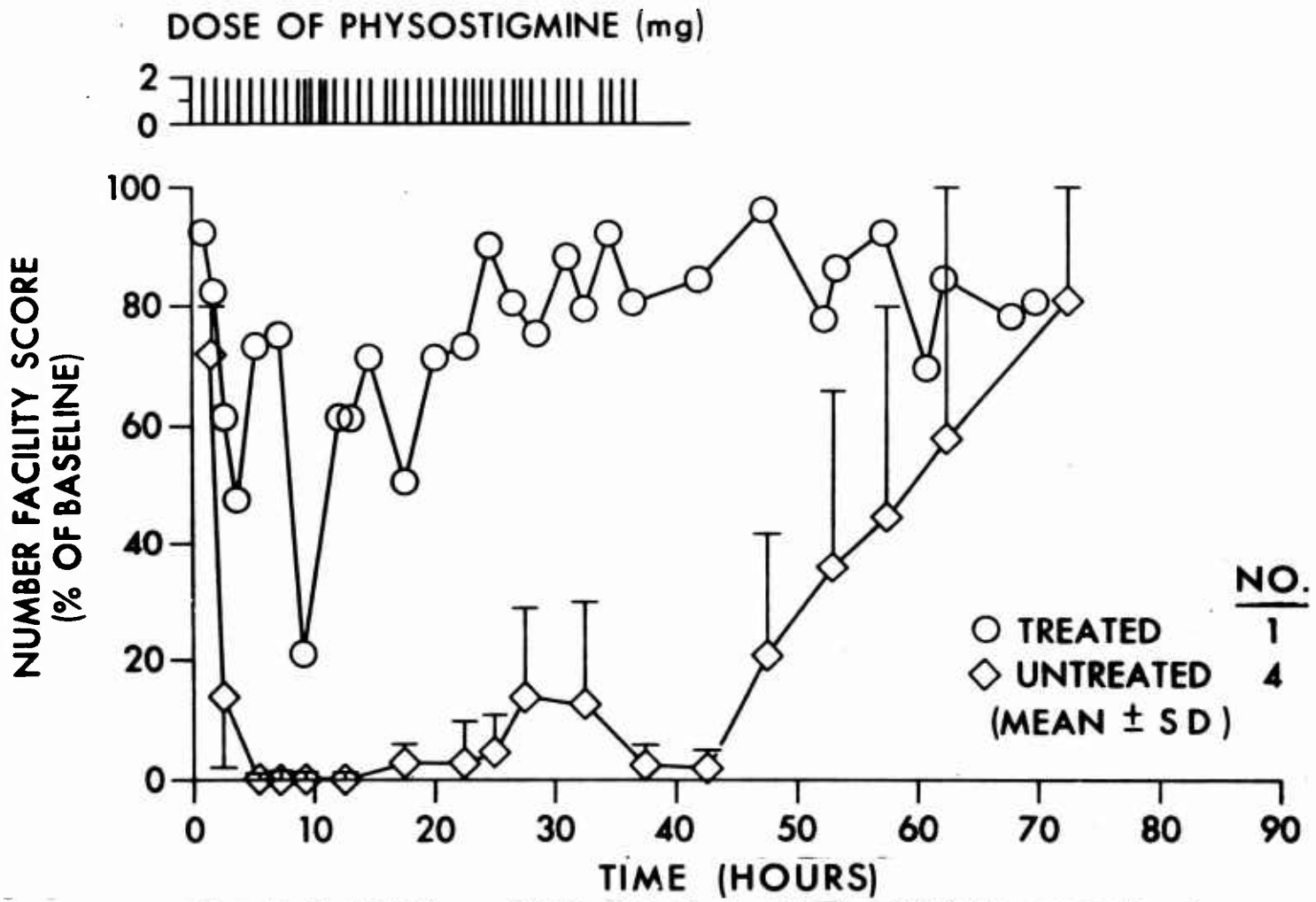

Figure 7. Serial NF Scores of Subject Who Received 7 μg/kg of QNB, Intramuscularly, and Was Treated with Physostigmine Orally, as Shown

For comparison, the mean scores of four subjects who received the same dose of QNB are shown.

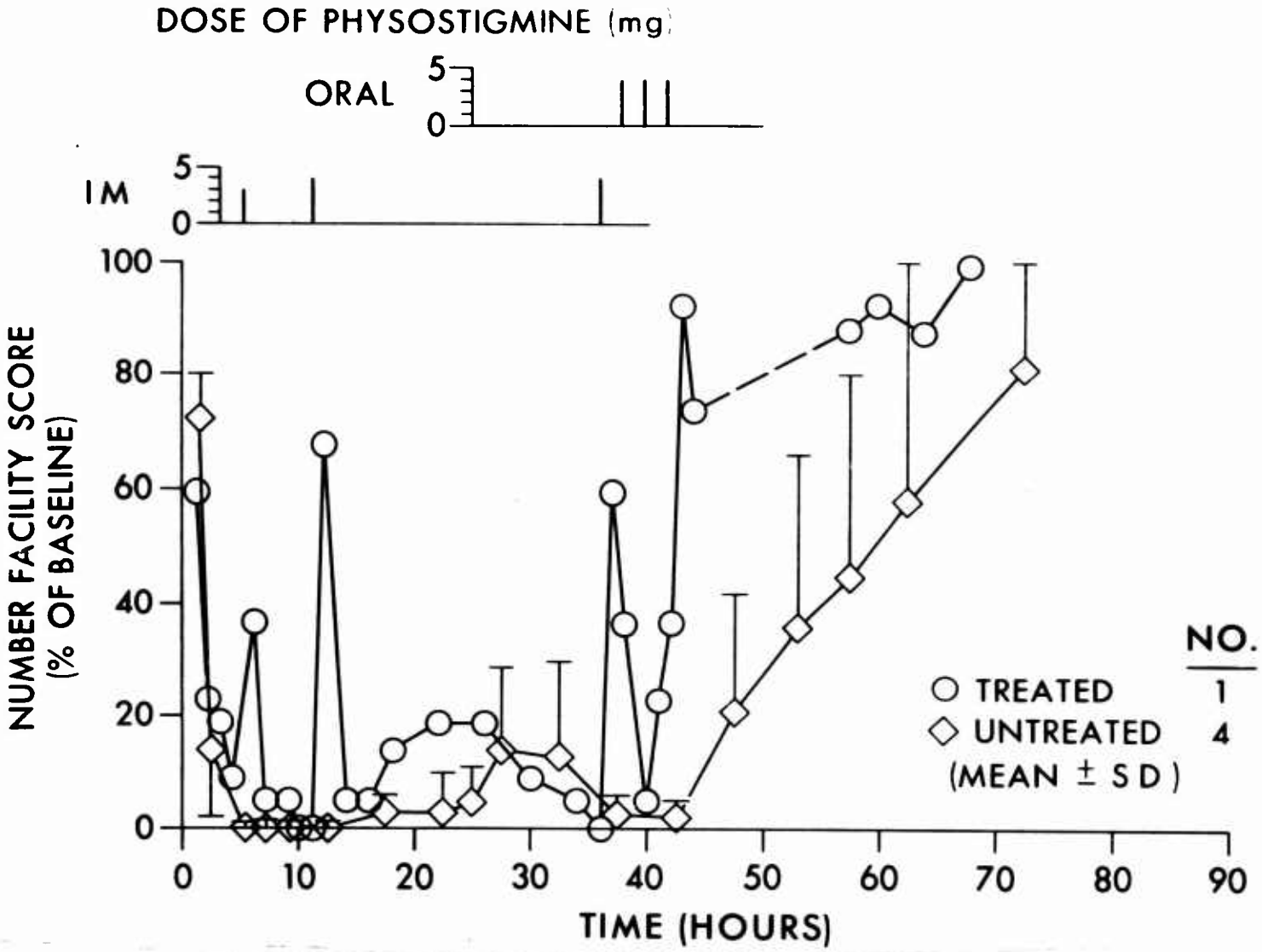

Figure 8. Serial NF Scores of Subject Who Received 7 μg/kg of QNB, Intramuscularly, and Was Treated with Physostigmine, Intramuscularly and Orally as Shown

For comparison, the mean scores of four subjects who received the same dose of QNB are shown.

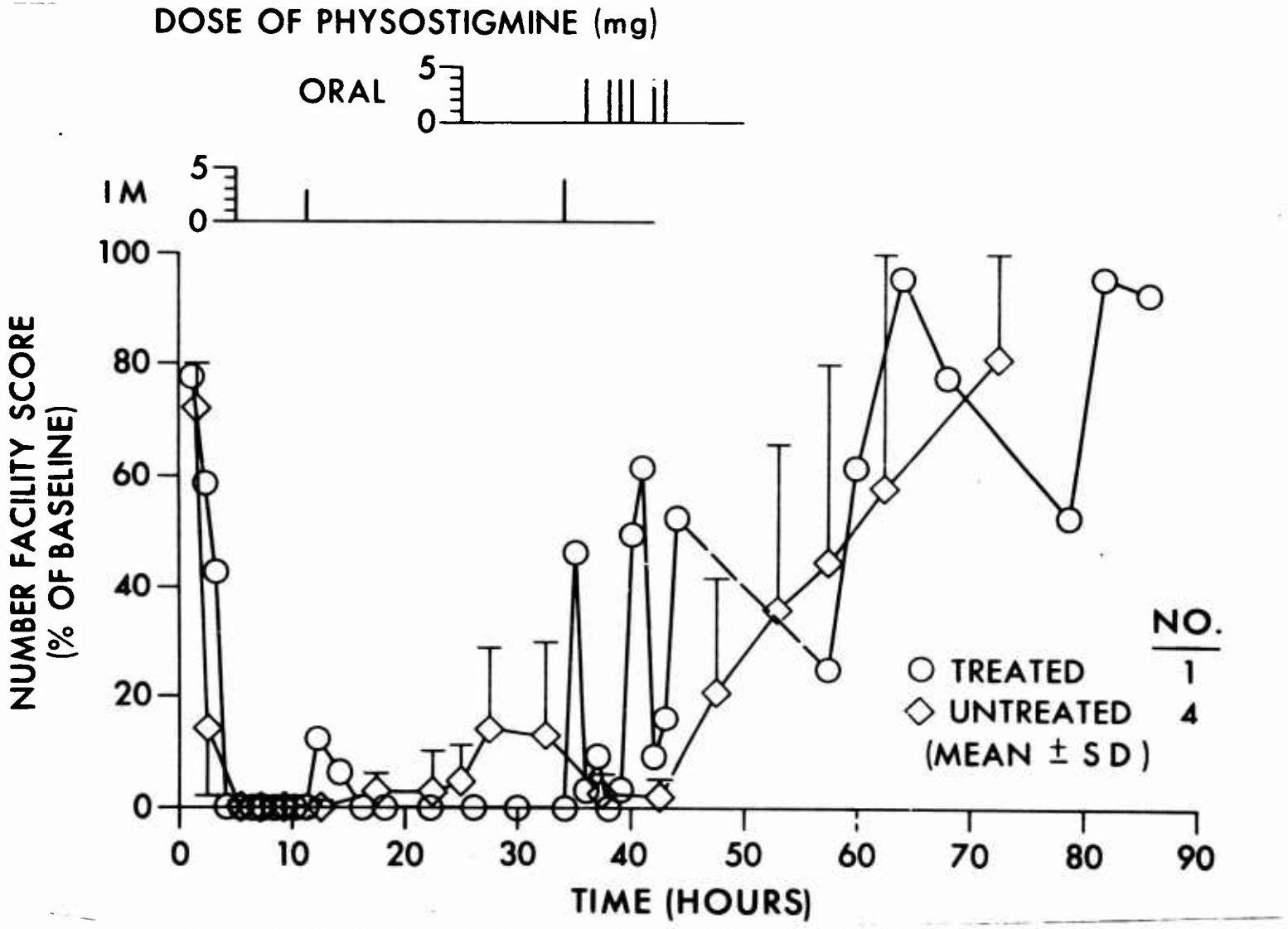

Figure 9. Serial NF Scores of Subject Who Received 7 μg/kg of QNB, Intramuscularly, and Was Treated with Physostigmine, Intramuscularly and Orally as Shown

For comparison, the mean scores of four subjects who received the same dose of QNB are shown.

The heart rates of the treated subjects were lower than those of the untreated. The first two subjects who were treated continually with oral physostigmine had an initial tachycardia which was less severe than that of the controls (120 to 12[illegible] versus 130 to 140 bpm), and thereafter their average heart rate was 10 to 20 bpm lower. In the third subject, the initial intramuscular dose of physostigmine, given 2 hours after QNB, caused a decrease in heart rate from 130 to 92 bpm during the hour after that dose. The rate increased to 100 bpm; the second dose of physostigmine, given 11 hours after QNB, caused a decrease to 80 bpm. This subject's heart rate remained about 70 bpm (versus 80 to 90 for the control subjects), further doses of physostigmine having no notable effect. The initial intramuscular dose of physostigmine, given 11 hours after QNB, also caused a drop in the heart rate of the fourth subject (110 to 75 bpm), but heart rate returned to the nontreated rate several hours later. This subject had no tachycardia at the time of subsequent doses of physostigmine (starting at 34 hours), but the second intramuscular dose caused a slight, transient decrease in rate (68 to 60 bpm).

IV. DISCUSSION.

In general, poisoning or overdosage by cholinolytic compounds does not represent the immediate problem in treatment that poisoning with certain other compounds, e.g., cyanide and cholinesterase inhibitors, does. In cases of mild-to-moderate overdosage, the question of whether to treat at all may arise because slight tachycardia, xerostomia, and a mild disordering of the mental status do not present a threat to life and are self-limited.

There are circumstances associated with poisoning by these compounds in which treatment is indicated: (1) The tachycardia may produce a strain on the cardiovascular system, particularly if the patient is elderly or has preexisting cardiovascular disease; (2) the reduction in ability to lose heat because of sweat inhibition may make the patient susceptible to heat exhaustion or heat stroke; (3) the patient, if delirious, may be difficult to handle and may present the hazard of doing physical harm to himself or others; and (4) a deepening sensorium or a comatose state indicates a severe disruption of vital processes. Ordinarily, such disruption is the only circumstance in which a therapeutic effect within minutes would make a significant difference. For the other conditions mentioned above, a delay of 15 to 20 minutes in the onset of therapeutic effect would not make a significant difference. If heat accumulation were the only problem, it would be more effectively reversed by moving the patient to a cool environment (70°F) and bathing him with cool fluids.

The only advantage of intravenous therapy with physostigmine over intramuscular or oral therapy is the faster onset of action. The patient's sensorium starts to clear and his heart rate starts to decrease in 2 to 5 minutes (in several instances, the change was apparent before the needle was removed from the vein), whereas this may not occur until 10 to 20 minutes after intramuscular administration.

There are definite drawbacks and disadvantages to the intravenous use of physostigmine. The recommended rate of administration is 1 mg per minute so that the physician must spend 1 to 4 minutes giving a dose. If repeated doses are required, this can become time consuming. It is not always possible to convince a restless, delirious patient to remain quiet with a needle in his vein this long and several other people may be needed to restrain him. The hazard of producing cardiac arrhythmias is not a minor problem. Since most cholinolytic compounds produce tachycardia, one must be aware of the risks of reducing the heart rate by 30 to 40 bpm over a several minute period. Some cholinolytics (e.g., scopolamine) cause bradycardia and one should approach with even

greater trepidation the intravenous administration of a vagotonic drug to a patient who already has a drug-caused bradycardia. Finally, convulsions have been reported after intravenous physostigmine was used to treat intoxication caused by a tricyclic antidepressant.[9]

In instances where a rapid onset of antidotal activity is not an overwhelming necessity, it seems preferable to administer physostigmine by a route causing less rapid absorption and thus decreasing the chances of an undesirably high plasma concentration occurring quickly. In approximately 100 instances of administering physostigmine intramuscularly, we have seen only two people who had toxic effects from this drug, and both had fine fasciculations of the platysma which lasted no longer than 10 to 15 minutes.

The rapid elimination of physostigmine from the body, with the corresponding short time of therapeutic activity, has been called a disadvantage of the drug.[9] On the contrary, we feel that the transient effect is advantageous. Any toxic effect of physostigmine will be short lived. Also, if doses are spaced properly, the physician can evaluate the patient and the need for more physostigmine before administering the next dose. This "titration" of antidote against the toxic effect of the original poison is analogous to administering insulin to a patient in diabetic coma. This allows the physician to judge the progress of the intoxication and also to change the dose or timing of physostigmine administration if necessary.

These and previous studies[3,4] indicate that physostigmine given intramuscularly or orally in proper dosage is a safe and effective antidote to poisoning by cholinergic blocking drugs. We have not seen severe cholinergic manifestations as a result of its use by these routes as have been reported after intravenous administration.[9,11]

We strongly recommend that the pharmaceutical industry provide preparations for use by these routes of administration.

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